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11/20/2006

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EXAMINER

SAIDHA, TEKCHAND

ART UNIT

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/572,976	<b>Applicant(s)</b> FROST, JOHN W.	
	<b>Examiner</b> Tekchand Saidha	<b>Art Unit</b> 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 10 July 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 23-30,38 and 46-60 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 23-30,38 and 46-60 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

**Final Rejection**

1. ***Election***

Applicant's previously elected Group V (claims 23-30) & the sequence of SEQ ID NO: 4 with traverse, in response filed 10/21/2008 is acknowledged.

2. The traversal was on the grounds of PCT Rule 13.1. In the least, the claims corresponding to Group V (claims 23-30) and Group VI (claim 38) should be examined together because of the common special technical feature present in these claims.

3. Accordingly, Applicants' arguments were considered and restriction requirement between groups V & VI was withdrawn.

4. Claims 23-30 & 38 and SEQ ID NO: 4 were considered in the previous examination.

5. Amendment and response filed 7/10/2009 is acknowledged. Claims 23-30, 38 & 46-60 are present. These claims will be considered with respect to **SEQ ID NO: 4**, the elected sequence in the response to Election/Restriction filed 10/21/2008.

6. Applicant's arguments filed with the amendment cited above, have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

7. Any objection or rejection of record not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

8. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. Claims 46, 52 & 54 are objected to because of the following informalities: Claims 46, 52 & 54 recite non-elected sequences of SEQ ID Nos. 2 & 6. Cancellation of non-elected subject matter is required.

10. ***Claim Rejections - 35 USC § 112*** (first paragraph)

***Written Description***

Claims 23-30, 38 and 46-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

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matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants are directed toward the USPTO Written Description Training Materials made available to the public on 04/11/2008 for information regarding examination of patent claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph.

According to MPEP 2163, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed.Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.

The method steps reciting the products must comply with the written description requirement. The claims are genus claims directed toward a method using a genus of 2-keto 3-deoxy 6-phosphogalactonate aldolase (KDPGal aldolase) from any source or any amino acid sequence and structure or a method using a genus of any "DHQ synthase" from any source, or the sequence of SEQ ID NO: 4 modified such that the sequence is at least 50% or 70% homologous to the sequence of SEQ ID NO: 4 or the specific mutations of I10V, V28L, V28M, S42T, V85A, V154F and F196I corresponding to SEQ ID NO: 4.

The scope of each genus includes many members such as KDPGal aldolase or synthase enzymes with widely differing structural, chemical, and physical characteristics. Furthermore, each genus is highly variable because a significant number of structural differences between genus members exists. Recitation of the name "KDPGal aldolase" and/or its source as a "*Klebsiella pneumoniae*", for example, do not define any structural features and amino acid sequences commonly possessed by the genus. The specification does not describe and define any structural features and amino acid sequences commonly possessed by each genus. There is no art-recognized correlation between the structures of the KDPGal aldolase from "*Klebsiella*

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pneumoniae” with the other KDPGal aldolases. Those of ordinary skill in the art would not be able to identify without further testing other specific KDPGal aldolases that can be used in the claimed method.

The instant specification discloses KDPGal aldolases of the sequences of SEQ ID Nos. 2, 4 & 6 as well as from *Agrobacterium*, *Bradyrhizobium*, *Brucella*, *Caulobacter*, *Escherichia*, *Klebsiella*, *Ralstonia*, *Salmonella*, and *Sinorhizobium*. However, these KDPGal aldolases are not representative of the genus of KDPGal aldolases or synthases being used in the method from being any source.

MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification fails to disclose additional KDPGal aldolases or synthases, encompassed by the claims. As such the disclosure of the above mentioned *species* is insufficient to be representative of the attributes and features common to all the members of each claimed genus. Thus, one skilled in the art cannot visualize or recognize the identity of the members of each claimed genus.

In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of the invention recited in claims 23-30, 38 & 46-60.

Applicants' arguments:

With reference to the Office Action that the KDPGal aldolase does not define any structural feature and amino acids commonly possessed by the genus, Applicants argue “that such detailed structural features are not required in the instant claims. The claims do require that the compound has the general framework of a polypeptide, but functional language (i.e., KDPGal aldolase activity) is permitted and can be used to define the subject matter sought to be claimed. See MPEP 2173.05(g). The written description guidelines do not require that a claim reciting a polypeptide having a specific enzymatic activity also recite a specific polypeptide sequence.

In relation to this (see paragraph 0060, page 18), Applicant notes the prior art describes that KDPGal aldolase activities have been identified in many different

microbial strains. Claim 23 recites that isolated KDPGal aldolases can be used in the claimed method, and such sources, (e.g. the bacterial strains as described and known to those in the prior art) provide written description supporting the claim.

Applicants' arguments are considered but not found to be persuasive because structure is required. The presence of prior art sequences of KDPGal aldolases from some bacterial or microbial sources do not provide support for aldolase sequences from any source. Further, the specific mutational modifications at positions I10V, V28L, V28M, S42T, V85A, V154F and F196I corresponding to SEQ ID NO: 4 resulted in measurable aldolase activity and identification of variant shikimate pathway capable of utilizing erythrose 4-phosphate (E4P) and pyruvate in the formation of 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP), as opposed to no or negligible activity (see Tables 2-4 of the instant specification).

Applicants provide sequence alignments of SEQ ID NO: 2, 4 & 6 and argue that a high homology exists among KDPGal aldolase sequences.

Applicants arguments are considered and found persuasive with respect to the specific bacterial sequences, however, are not representative of KDPGal aldolases from any source. Further, the instant specification does not provide examples or data of KDPGal aldolases activities from other sources, such as animals, plants, fungi, yeast, etc., capable of catalyzing the condensation of pyruvate and E4P to DAHP.

Citing " Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005), which is used in MPEP to guide analysis of written description of claims towards chimeric gene formed from an antibody variable domain protein sequence and a lymphocyte activation protein sequence. The Board (of Patent Appeals and Interferences of the USPTO) originally decided that the claim to the sequence lack patentability because the specification did not set forth the complete sequence of the chimeric gene. However this decision was remanded by the Federal Circuit court who determined that the Board misconstrued the precedent and failed to consider the state of knowledge and the science, which included knowledge of the sequences to be combined.

The court in *Capon* noted that the specification disclosed primer sequences that could be used to generate the gene sequences of interest, that such sequences can be isolated and joined by conventional methods (PCR or cloning by primer repair), and discussed various known procedures for identifying, obtaining, and linking DNA segments. The Board did not dispute that these methods could be carried out to provide the claimed sequences. In agreement with the precedent of *Capon*, KDPGal aldolases from a variety of other *bacterial strains* could be identified using conventional methods and known procedures given the extensive guidance provided by the specification and the showing of high degrees of homology.

The fact pattern of this case is distinct from the fact pattern of *Capon* case because of the differences in technologies. While 'primer sequences' are known to aid in fishing out or generate the gene sequences of interest, specific mutations or modified bacterial KDPGal aldolase sequences capable of a novel condensation reaction cannot necessarily be extrapolated to any KDPGal aldolase that can be obtained from any source even if the KDPGal aldolases are known because the small species of KDPGal aldolases disclosed and exemplified in the method is not representative of the genus claimed. The rejection is therefore maintained.

11. ***Enablement Rejection***

Claims 23-30, 38 and 46-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for converting pyruvate and E4P to DAHP, comprising contacting an isolated or recombinant KDPGal aldolase of sequence of SEQ ID NO: 4 or the specific mutants thereof with a solution containing pyruvate and E4P, does not reasonably provide enablement for a method for converting pyruvate and E4P to DAHP, comprising contacting any isolated or recombinant KDPGal aldolase from any source with a solution containing pyruvate and E4P (claim 23). Claims 24-30 & 38, have added limitation wherein the method comprise DHQ synthase from any source (claim 24); DHQ hydratase (claim 25); wherein the method is performed within a recombinant cell (claim 26); wherein said host cell is produced by transforming the cell with nucleic acid encoding at least one of a KDPGal aldolase or a DHQ synthase; wherein said recombinant cell contains at least one recombinant

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transketolase or at least one recombinant transaldolase (claim 28); Use of a recombinant KDPGal aldolase to produce DAHP from pyruvate and E4P (claim 29); wherein said use further includes use of a recombinant DHQ synthase to produce DHQ from said DAHP (claim 30); and the process of preparing DAHP and intermediate compounds of the shikimate pathway, viz., DHQ and DHS. Claims 47-49 depend on claim 29 and add further limitations wherein the contacting step is performed *in vivo*, or in solution, or wherein the aldolase has a specific activity of 0.3-1.3 U/mg. Claims 46 & 50-60 add further limitations of a sequence and wherein the sequence of SEQ ID NO: 4 is modified such that the sequence is at least 50% or 70% homologous to the sequence of SEQ ID NO: 4 or has the specific mutations of I10V, V28L, V28M, S42T, V85A, V154F or F196I corresponding to SEQ ID NO: 4.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of enzymes, including variants, broadly encompassed by the method claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of SEQ ID Nos. 2, 4 and 6 and the specific mutations. Regarding, the derivative(s) resulting from the catalysis of the enzymatic reaction of the method (claim 38), the specification provide no guidance to one skill in the art to make derivatives by the process disclosed. The various compounds formed are mere intermediates of the pathway.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the



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instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of any KDPGal aldolase with 50% or 70% homology to the enzymes of SEQ ID NO: 4, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting KDPGal aldolase activity; (B) the general tolerance of KDPGal aldolase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any KDPGal aldolase residues with an expectation of obtaining the desired enzymatic function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of exact nature of the encoding DNA (or polynucleotide) encoding KDPGal aldolase of varying homologies to prepare the recombinant host cells and the encoding of specific pathway enzymes of known substrate specificity having the desired enzymatic characteristics in order that be used in the method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants Arguments:

Applicants argue that "With regard to enablement, the Office has stated that the disclosure is limited to the polypeptide sequences of SEQ ID NO: 2, 4, and 6. This assertion by the Office is also incorrect. Enzyme activity was demonstrated for twenty-

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one other KDPGal aldolase sequences that were identified from the directed evolution experiments of the *E. coli*, *K. pneumoniae*, and *S. typhimurium* dgoA sequences (see paragraph 0071, page 27). Enzyme activity was also shown for KDPGal aldolase sequences identified in the DgoA family shuffling method. As disclosed in page 29, lines 24-26, the DgoA family shuffling produced another batch of seventy- two other KDPGal aldolase sequences that were analyzed.

While the Office has stated recombinant methods are known, it has also asserted that it is not routine in the art to screen for multiple substitutions or modifications as encompassed by the instant claims. However, as shown by the extensive experimental data as mentioned herein, the current application has indeed screened for multiple substitutions or modifications and identified a significant number of variants that have enzymatic activity. Using this information, the specification provides a guide to make additional variants having activity as well.

Applicants' arguments are considered but not found to be persuasive because the language used in the claims do not support or correspond to arguments presented here. The claims lack the source of the aldolase as well as the structure as not every KDPGal aldolase from any source or KDPGal aldolase of SEQ ID NO: 2, 4 or 6 that can be modified by 30-50% have been shown to catalyze the formation of DAHP from pyruvate and E4P. Prior art may provide numerous sequences of KDPGal aldolase from a wide range of sources – however, prior art or the instant specification fail to provide evidence or support the scope of the instant method claims. Specific mutations of I10V, V28L, V28M, S42T, V85A, V154F or F196I (seven positions) corresponding to SEQ ID NO: 2, 4 & 6 (related sequences) are provided. However, a skilled artisan cannot reasonably extrapolate these specific mutations to include modifying any KDPGal aldolase from any source in order to convert pyruvate and E4P to DAHP for all the reasons discussed in the rejection.

Recent case law also supports enablement of the present claims. For example, *Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co.* (228 F.3d 1338, 56 USPQ2d 1332; Fed. Cir. 2000), dealt with claims to a method for genetically modifying a bacterium to produce an amino acid. The method involved mutation of a bacterium to a donor strain,

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isolating the mutated gene from the bacterium, inserting the mutated gene into a recipient strain with mutations in both amino acid synthesis and metabolism genes. An accused infringer argued that the claims could cover a myriad of bacterial strains not yet known, however the court, in response, stated that the claims were enabled. "According to the record, all of the methods needed to practice the invention were well known to those skilled in the art. Despite the diversity existing among bacteria, practitioners of this art were prepared to carry out the identification, isolation, recombination, and transformation steps required to practice the full scope of the claims.

Applicants' arguments are considered but not found to be persuasive because the method in question is amenable to modification because inserting a mutated bacterial gene into another bacterium is a fairly routine procedure in the art. However, this is not relevant to the claims in question.

Citing another case [Falkner v. Inglis (448 F.3d 1357; Fed. Cir. 2006)], Applicants argue that the case - dealt with a method for inactivating an "essential" gene in a poxvirus vector. The patent set forth no working example or gene sequence. However, prior art publications described the poxvirus genome and the locations of "essential regions." Testimony indicated that one skilled in the art would have been able to locate an "essential" gene, even though that may have required extensive time and expense.

In yet another recent case pertaining to enablement, Monsanto Co. v. Scruggs (459 F.3d 1328; Fed. Cir. 2006), dealt with claims to insertion of synthetic gene, including a "CaMV" promoter, into plant DNA. The patents did not "cover one particular gene sequence," and the DNA sequences of several promoters were known in the art. An accused infringer asserted on appeal that the patent was invalid for not satisfying the enablement requirement. The accused infringer argued that the patent was not enabling because no particular gene sequence is claimed and because only one example of the entire genus of CaMV promoters is described in the specification.

While these are biotechnology cases it is not clear how these case are relevant to the claims present here as no comparison of the fact pattern is presented between the cited cases and the instant case under prosecution.

The rejection is maintained for all the reasons discussed above.

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12. Claims 59 & 60 recites the limitation "wherein said native bacterial KDPGal aldolase.." in claim 50. There is insufficient antecedent basis for this limitation in the claim.

13 No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached between 8.30 am - 5.00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272 0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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